DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

94238d

CBER-01-012

February 9, 2001

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Roberta McKee, Ph.D.
Vice-President of Vaccine & Sterile Quality Operations
Merck & Co., Inc.
P.O. Box 4
Sumneytown Pike
West Point, Pennsylvania 19486

Dear Dr. McKee:

The Food and Drug Administration (FDA) conducted an inspection of your facility located at Sumneytown Pike, West Point, Pennsylvania, between August 14 and October 11, 2000. During the inspection, our investigators documented significant deviations from the applicable standards and requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21 Code of Federal Regulations (21 CFR), Parts 211 and 600-680 as follows:

1. Failure to follow an appropriate written testing program designed to assess the stability characteristics of drug products and to include test intervals for each attribute examined to assure valid estimates of stability [21 CFR 211.166(a)] in that:

   a. Varicella Virus Vaccine Live (Varivax) stability potency tests have not been completed on schedule. For example:
      i. Lot 0624655 24-month stability time point has been pending since November 1999.
      ii. Lot 0628694 18-month stability time point has been pending since May 2000.
      iii. Lots 0629251, 0629258, and 0629609 18-month stability time points have been pending since June 2000.
      iv. Lot 0631073 15-month stability time point has been pending since June 2000.

v. Lot 0634482 0-month and 3-month stability time points have been pending since February 2000.
vi. Lots 0500870 and 0500871 18-month stability time points have been pending since February 2000.
vii. Lot 0500872 18-month stability time point has been pending since March 2000.

b. Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine (Comvax) stability mouse potency tests have not been completed on schedule. For example:

i. Lot 0632508 12-month stability time point has been pending since May 2000.
ii. Lot 0636682 1-month stability time point has been pending since May 2000.

These stability mouse potency tests were completed in August 2000.

2. Failure to maintain written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to posses and to assure that such procedures, including any changes, are drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by quality control [21 CFR 211.100] in that:

a. There is no procedure for maintaining, controlling, and issuing "insert sheets" used to document additional process steps as documented in a Change Request or Atypical Process Report.

b. There is no procedure that describes or authorizes the use of change requests with "partial approval."

3. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications or extend the investigation to other batches that may have been associated with the specific failure or discrepancy [21 CFR 211.192]. For example, investigations into the failure of Varivax packaging lot 1839H (fill lot 0626404), Test Failure Investigation #99-063 and Atypical Process Report 1999-3000-0014, found no assignable cause and concluded that the failure to meet post-packaged potency specifications was part of the expected random 5% failure rate for the Varicella dilution model. However, the investigations do not cross-reference or extend to the failure investigation of lot 0626404, initially filled as part of validation study PVP97-185, which failed potency specification in three out of five validation samples.

4. Failure to establish and follow control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR 211.110(a)] in that:

a. Varicella Final Dilution Calculation standard operating procedure (SOP) 209-203X, does not include the adjustment factor range used to adjust the measured bulk potency to ensure that final formulations meet potency requirements.

b. Bulk media challenge procedures do not include provisions for aborting or invalidating bulk media challenges. Since January 1999 seven bulk media challenges have been aborted or invalidated.

5. Failure to exercise appropriate controls over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel [21 CFR 211.68(b)] in that:

a. There is no policy or procedure in place that identifies laboratory [redacted] access privileges for specific job descriptions.

b. SOP 223-LM901, "Creating a [redacted] Account, Modifying Requirements and Disusering Accounts" requires that an account be "disusered" if the employee will no longer be using the [redacted] and requires changing the account requirements if the user's need change. However, the Biological Quality Assurance Manager, who no longer works in the laboratory, still has access to test data entry (security level [redacted]).

6. Failure to describe in an annual report any changes in the production process or test methods that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they relate to the safety or effectiveness of the product [21 CFR 601.12(d)] in that the Director, Center for Biologics Evaluation and Research was not notified of the change in passage level of [redacted] cells used for potency determination of Measles and Mumps Virus Vaccines.

7. Failure of batch production and control records to include an accurate reproduction of the appropriate master production or control record [21 CFR 211.188(a)] in that media challenges performed in December 1999 and July 2000 were documented in batch records, which were copied from an obsolete version of the master production record dated March 4, 1998, instead of the current version dated July 15, 1998.

We acknowledge receipt of your responses dated October 24, 2000, and January 15, 2001, to the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letters may be referenced in your response to this letter, as appropriate. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA 483:

FDA 483 observation 1

Your response indicates that depressed measles potency values were observed upon implementation of a new cell bank. New cell banks should be qualified before use according to a written procedure.

FDA 483 observation 3

Regarding the Mumps Virus Vaccine Live stability data, your response indicated the stability profile of each lot was within the expected range based on historical trends. Products must meet their specifications, not the historical trend throughout the labeled expiry period.

Our investigators reported that the data in your firm's files showed that a number of Mumps Vaccine stability samples representing lots manufactured before the formulation was changed during February 2000 failed to meet the minimum potency specification. Product manufactured before February 2000 may still be on the market because the expiry period is two years. Please submit an analysis of Mumps stability data describing the range of potencies you would expect the various Mumps Vaccine products to reach at the two-year expiration date. For the analysis, assume the initial potency is the minimum release potency specification that was in effect before February 2000. Please summarize the available data regarding product efficacy at the lower end of this potency range.

Regarding your investigation of the Mumps Vaccine stability test failures, it did not include analyses of reserve samples of additional batches. One batch of each different presentation was placed on the stability-monitoring program every year. This stability batch is a sample, which represents the many batches that are manufactured during the year. When the designated stability batch fails to meet its specification, the investigation should include examination of reserve samples of other batches to quickly determine whether the out of specification result represents an anomaly or a serious problem.

FDA 483 observation 7

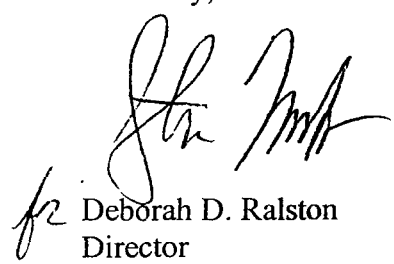
It appears from our investigator's report that master records are not always updated when processes are changed. SOP's 299-100X "dated 5/12/00 and 300-333 dated 5/19/00 allow handwritten changes which have not been incorporated into the master records to be made to batch records. SOP's 299-119X dated 12/17/99 and 300-148X dated 9/10/99 indicate master records are evaluated every three years. Please describe what triggers an updating of master records and limitations on the process of changing the copy of the master record to generate individual batch records.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. It is your responsibility to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and all applicable regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

Please notify this office in writing, within 15 working days of receipt of this letter, of any additional specific steps you have taken to correct the noted deviations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include license suspension and/or revocation.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality, HFM-600, Suite 200N, 1401 Rockville Pike, Rockville, MD 20852-1448.

Sincerely,



for Deborah D. Ralston
Director
Office of Regional Operations